

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification 5 :</b> A61K 9/48, 9/66, 47/10 A61K 31/55		<b>A1</b>	<b>(11) International Publication Number:</b> WO 91/07950 <b>(43) International Publication Date:</b> 13 June 1991 (13.06.91)
<b>(21) International Application Number:</b> PCT/GB90/01821			<b>(74) Agents:</b> WOODS, Geoffrey, Corlett et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).
<b>(22) International Filing Date:</b> 23 November 1990 (23.11.90)			<b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), IT (European patent), LU (European patent), NL (European patent), NO, SE (European patent).
<b>(30) Priority data:</b> 8926612.6 24 November 1989 (24.11.89) GB			<b>Published</b> <i>With international search report.</i>
<b>(71) Applicants:</b> FARMITALIA CARLO ERBA LIMITED [GB/GB]; Italia House, 23 Grosvenor Road, St. Albans, Herts. AL1 3AW (GB). RP SCHERER LIMITED [GB/GB]; Frankland Road, Blagrove, Swindon, Wilts. SN5 8YS (GB).			
<b>(72) Inventors:</b> LAUNCHBURY, Alfred, Paul ; 51A Station Road, New Barnet, Herts. EN5 1PR (GB). MORTON, Frank, Samuel, Short ; 8260 141st Street North, Seminole, FL 34646 (US). ROWE, Dennis ; 19 Branscombe Drive, Wootton Bassett, Swindon, Wilts. SN5 8HR (GB).			
<b>(54) Title:</b> PHARMACEUTICAL COMPOSITIONS			
<b>(57) Abstract</b> <p>A pharmaceutical unit dosage form is disclosed which comprises a soft gelatin capsule shell or a two-piece hard gelatin capsule and a fill comprising a benzodiazepine dissolved or suspended in a gel, wherein the gel has a drop point (C), prior to encapsulation, of at least 46 and comprises at least 63 % of polyethylene glycol 600, at least 4 % by weight of polyethylene glycol 4000 or 6000 and at least 21 % by weight of an intermediate polyethylene glycol. The gel fill used in the present invention cannot be expelled from a syringe at ambient temperature, and therefore removes the convenience to intravenous drug abusers of a capsule containing a drug dissolved or dispersed in a liquid filling. The capsule fill retains good bioavailability and pharmacokinetic properties.</p>			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	ML	Mali
AU	Australia	FR	France	MN	Mongolia
BB	Barbados	CA	Gabon	MR	Mauritania
BE	Belgium	GB	United Kingdom	MW	Malawi
BP	Burkina Faso	GN	Guinea	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	SD	Sudan
CF	Central African Republic	KP	Democratic People's Republic of Korea	SE	Sweden
CG	Congo	KR	Republic of Korea	SN	Senegal
CH	Switzerland	LI	Liechtenstein	SU	Soviet Union
CI	Côte d'Ivoire	LK	Sri Lanka	TD	Chad
CM	Cameroon	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark	MG	Madagascar		
ES	Spain				

- 1 -

PHARMACEUTICAL COMPOSITIONS

The present invention relates to improvements in and relating to pharmaceutical compositions in unit dosage form.

Temazepam is a benzodiazepine with a combination of 5 properties which have secured its widespread clinical acceptance as a hypnotic and oral premedicant. It has sleep inducing and anxiolytic properties, low toxicity (the oral LD 50 in mice is almost 1000mg/kg), no active metabolites, a short half life and no significant drug interactions. Both 10 the efficacy of the drug as a hypnotic/premedicant, and prompt clearance of the drug to give early recovery and avoid "hangover" characteristics, depend upon rapid and complete absorption.

Both hypnotic and premedicant activity are dependant on 15 the rate of rise of drug blood levels, a rapid steep rise being essential. Conventional formulations of temazepam in tablets or hard gelatine capsules, which depend on dissolution of temazepam powder in the gut, are therefore not suitable. For this reason, a softgel capsule comprising 20 temazepam dissolved in a liquid hydrophilic fill was developed. This formulation, containing temazepam dissolved in the water miscible solvent polyethylene glycol 400 (PEG 400), permitted the drug to be completely absorbed within 40 to 60 minutes, resulting in prompt sleep induction or 25 premedicant anxiolysis. The early completion of the absorption phase also permitted a subsequent steep fall in

- 2 -

blood levels (half life about 1.3 hours) during the distribution phase, which was responsible for the early smooth recovery seen with this drug. It also resulted in an elimination half life of 8 to 10 hours.

5 This combination of desirable properties led to wide clinical acceptance of the liquid filled temazepam softgel capsule. However, there have recently been reports that the liquid fill of the capsules lends itself to use by intravenous drug abusers. It also became apparent that it  
10 was the convenience of the liquid fill, and not an inherent attractiveness of temazepam itself, that lay behind the growing abuse.

Against this background a way of formulating temazepam was sought which would meet the criteria of removing the  
15 convenience afforded to drug abusers by the original fill liquid, whilst retaining the good bioavailability and pharmacokinetic properties of the drug. A further criterion was that the eventual solution adopted should be "non-punitive". The existence of potential sclerosants in the  
20 capsule fill was therefore to be avoided, because of the hazard this would present to the persistent intravenous drug abuser who, despite all possible deterrents, nevertheless managed to inject the new formulation.

A variety of options presented themselves, but were  
25 rejected:

(a) Suspension of the temazepam in a variety of thick

- 3 -

lipophilic carriers reduced the potential for abuse, but failed to give the required rapid dissolution profile.

(b) Colloidal silicon dioxide was identified as a potential gelling agent for the original fill liquid, but in 5 order to obtain a capsule fill of the required viscosity some 12 to 15% silicon dioxide was required. The strength of the gel was found to be highly dependant on the quantity of water present, which made the manufacture of reproducible gels difficult. The release of temazepam from such fills 10 was in any event found to be poor.

(c) Polyvinylpyrrolidone was identified as a further potential gelling agent. However, it was found to be difficult to achieve reproducible gelling with this material.

15 (d) The possibility of using a neutralised carbomer was examined. This had the potential for allowing a gel to be produced which would be difficult to syringe at neutral pH, but would still allow rapid drug release at gastric pH. However, manufacturing problems were encountered with this 20 option owing to time dependant viscosity increases. Also, the dissolution of temazepam from these mixes was inferior to dissolution from the original liquid-fill product owing to the slow reversal of the gel at gastric pH.

There is now provided, in accordance with the present 25 invention, a pharmaceutical unit dosage form comprising a soft gelatin capsule shell or a two-piece hard gelatin

- 4 -

capsule and a fill comprising a benzodiazepine dissolved or suspended in a gel, wherein the gel has a dropping point (C), prior to encapsulation, of at least 46 and comprises at least 63% by weight of polyethylene glycol 600, at least 2% 5 by weight of polyethylene glycol 4000 or 6000 and at least 21% by weight of an intermediate polyethylene glycol, the total amount of polyethylene glycol in the gel being 100%.

It is highly surprising in several respects that the present invention meets the various criteria set out 10 earlier. Firstly, previous attempts to thicken the original liquid capsule fill of PEG 400 with higher molecular weight polyethylene glycols had resulted in formulations which were still capable of being expelled from a syringe at ambient temperature. It was therefore not to be expected that a 15 composition comprising a major proportion of a low molecular weight polyethylene glycol as base could be rendered non-injectable.

Secondly, it was not to be predicted that polyethylene glycol 6000 would be suitable as a thickener because in 20 general, when dissolved in a lower molecular weight polyethylene glycol, PEG 6000 tends to crystallise out. The effect of this is to diminish the viscosity of the solution. It was found, however, that the combination of an intermediate polyethylene glycol with the higher molecular 25 weight polyethylene glycol and the base polyethylene glycol reduces the tendency of the higher PEG to crystallise whilst

- 5 -

not adversely affecting viscosity or drug dissolution.

The polyethylene glycols forming the gel are polymers of the general formula  $H(OCH_2CH_2)_nOH$  and are commonly referred to as macrogols, or PEGs. The number following each 5 polyethylene glycol corresponds to its average molecular weight. Thus polyethylene glycol 600 (or PEG 600) has an average molecular weight range of from 570 to 630; polyethylene glycol 4000 (PEG 4000) has an average molecular weight range of from 3700 to 4500; and polyethylene glycol 10 6000 (PEG 6000) has an average molecular weight range of from 5600 to 7000.

By "intermediate" polyethylene glycol is meant a PEG having an average molecular weight between 600 and 4000. One example is polyethylene glycol 1500 (PEG 1500) which has 15 a molecular weight range of from 1300 to 1600.

The amount by weight of PEG 600 in the gel is at least 63% by weight, for example from 63 to 75% or from 65 to 75% by weight. Other suitable ranges include from 65 to 73%, from 67 to 70% and from 67 to 68%. An amount of from 67 to 20 68% by weight of PEG 600 is particularly preferred.

The amount of PEG 4000, when present in the gel, is at least 2% by weight, for example from 2 to 12%, or from 4 to 10% by weight. An amount of from 7 to 10% by weight of PEG 4000 is particularly suitable.

25 The amount of PEG 6000, when present in the gel, is at least 2% by weight, for example from 2 to 7% or from 4.3 to

- 6 -

6.9% by weight. An amount of from 4 to 6% by weight of PEG 6000 is particularly suitable.

At least 2% by weight of PEG 6000 in the gel is generally preferable to at least 2% by weight of PEG 4000.

5 The intermediate polyethylene glycol is present in the gel in an amount of at least 21% by weight, for example from 21 to 33% or from 25 to 30% by weight. Other suitable ranges include from 21 to 30%, from 22 to 29% and from 25 to 28%. An amount of from 27 to 28% by weight of PEG 1500 is  
10 particularly preferred.

Examples of two preferred gel formulations are:

- (i) PEG 600, 68.0%; PEG 1500, 28.0%; PEG 6000, 4.0%; and
- (ii) PEG 600, 65%; PEG 1500, 25%; PEG 4000, 10%.

The gel consisting of the polyethylene glycol blend has a  
15 drop point of at least 46C before it is encapsulated in the unit dosage form of the invention. Owing to the nature of the encapsulation process, the drop point is no greater than 75C. Typically it has a maximum value of 60C, more preferably 50.3C. Typically the drop point is at least 48C,  
20 for example at least 48.2C. Preferably it lies in the range of 48C to 60C, for example 48.2C to 50.3C. The drop point is the temperature at which the gel, when suspended in solid form and heated, begins to drop. It may be measured using a standard Mettler FP83 dropping point apparatus using a sample  
25 cup conforming to DIN 51801. Heating rate 1°C per minute.

The fill may further comprise conventional ingredients

- 7 -

such as glycerol, other co-solvents such as propylene glycol, or colorants, e.g. pigments or dyes. When glycerol is included, it is typically present in an amount of from 2 to 20%, for example from 3 to 15%, preferably from 4 to 12%,

5 more preferably from 4.5 to 8% by weight based on the fill prior to encapsulation. As will be discussed, the glycerol content of the fill tends to rise after encapsulation owing to migration of a small amount of glycerol from the shell to the hydrophilic fill.

10 In a preferred embodiment of the present invention the fill includes chlorophyll, since the green coloration that this imparts to the capsule contents provides a visual deterrent to would-be drug abusers. The amount of chlorophyll used should be sufficient to make the capsule

15 contents deep green. In a 10mg temazepam capsule containing approximately 300mg of fill, this typically means an amount of from 0.2 to 0.3mg chlorophyll.

The capsule shell comprises gelatin. It is either a conventional two-piece hard gelatin capsule or a soft

20 gelatin capsule shell. The soft gelatin capsule shell further comprises a plasticiser for the gelatin, such as glycerin, propylene glycol or sorbitol. The plasticiser is suitably present in an amount of from 10 to 40% by weight, for example from 12 to 35% by weight, more preferably from

25 15 to 25% by weight.

The soft gelatin capsule shell typically further

- 8 -

incorporates an embrittlement inhibiting composition comprising sorbitol in admixture with one or more sorbitans and, possibly, other polyhydric alcohols. The amount of sorbitol/sorbitan(s) in the shell is suitably from 4 to 25% 5 by weight, for example from 6 to 20% by weight, preferably from 9 to 15% by weight. When other polyhydric alcohols are present the total amount of sorbitol and sorbitan in the embrittlement inhibiting composition is suitably from 45 to 75% by weight, for example from 55 to 66% by weight. The 10 other polyhydric alcohols are typically hydrogenated saccharides.

Suitable materials for introducing the embrittlement inhibiting composition into the soft gelatin capsule shell are concentrated aqueous solutions of polyhydric alcohols 15 derived from the hydrolysis and partial hydrogenation of glucose syrup. Examples thereof include the commercially available material sold under the Trade name "Anidrisorb 85/70". This product has the following typical analysis.

Components (\* by weight of concentrated aqueous solution)

20	D-Sorbitol	Sorbitans	Other polyols	Mannitol	Water
	24-45	20-30	20-25	0-6	13-20

The capsule shell, whether hard or soft, suitably also comprises other conventional ingredients such as colouring

- 9 -

agents (pigments or dyestuffs), anti-oxidants or preservatives. It is particularly preferred in the present invention to include chlorophyll in the shell to maintain product identity with the original liquid filled capsules.

5 The chlorophyll is suitably present in the soft gelatin shell in an amount of from 0.05 to 0.5% by weight, in particular from 0.08 to 0.3% by weight, more preferably about 0.1% by weight. A suspension of TiO<sub>2</sub> in glycerol is also suitably included in the soft gelatin shell, the ratio 10 of TiO<sub>2</sub> to glycerol typically being of the order of 1:3. Such a suspension suitably forms from 0.5 to 2% by weight of the soft gelatin capsule shell, more preferably about 1% by weight.

Any member of the benzodiazepine group of compounds may 15 be dissolved or suspended in the polyethylene glycol gel and encapsulated in the hard or soft gelatin capsule shell. Temazepam is a preferred benzodiazepine for use in the present invention.

The invention further provides a process for preparing a 20 pharmaceutical unit dosage form as hereinbefore defined which process comprises

(a) preparing a polyethylene glycol blend by combining at least 63% by weight of polyethylene glycol 600, at least 2% by weight of polyethylene glycol 4000 or 6000 and at 25 least 21% by weight of an intermediate polyethylene glycol,

(b) forming a fill by dissolving or suspending a

- 10 -

benzodiazepine in the polyethylene glycol blend, and

(c) encapsulating the fill in a soft gelatin capsule shell or a two-piece gelatin capsule.

The blend of polyethylene glycols for the gel of the  
5 capsule filling is prepared by a standard method, typically  
involving combining the three components of different  
molecular weight in a jacketed mixing vessel maintained at a  
temperature equal to, or above, the melting point of the  
highest molecular weight polyethylene glycol. For example,  
10 the polyethylene glycol 600 is placed in a jacketed mixing  
vessel, to which the intermediate polyethylene glycol, such  
as polyethylene glycol 1500, and either polyethylene glycol  
4000 or polyethylene glycol 6000 are added. The mix is  
heated to about 75°C, with stirring. Stirring is then  
15 continued at this temperature until a clear solution is  
obtained.

Glycerol may be included with the polyethylene glycol  
blend in the capsule fill. It is suitably introduced into  
the fill by being combined with the polyethylene glycol  
20 blend. Typically, it is introduced into the jacketed mixing  
vessel together with the intermediate polyethylene glycol  
and the polyethylene glycol 4000 or 6000, the mixture then  
being stirred until a clear solution is obtained. Other co-  
solvents, for example propylene glycol, may also be  
25 introduced in this way.

The capsule fill is prepared by combining the

- 11 -

polyethylene glycol blend, optionally including glycerol and/or one or more other co-solvents, with the benzodiazepine. Typically, the benzodiazepine is simply stirred into the molten polyethylene glycol blend contained

5 in the jacketed mixing vessel, the blend having been brought to a temperature of about 65°C. Stirring is continued until the benzodiazepine has completely dissolved or has become homogeneously suspended, which typically takes from 5 to 15 minutes. Once the benzodiazepine has fully dissolved the

10 mixture may be deaerated, by applying a vacuum to the jacketed mixing vessel. When deaeration is complete, the vacuum is broken, and the mixture for the capsule fill is transferred to a thermostatically controlled jacketed vessel.

15 When it is desired to introduce chlorophyll into the capsule fill, the chlorophyll is suitably dissolved in warm, purified water to form a solution and this chlorophyll solution is then added to the mixture of benzodiazepine and polyethylene glycols in the jacketed vessel, prior to

20 deaeration. Deaeration is suitably then carried out as described above.

When a conventional two-piece hard gelatin capsule is used, the unit dosage form of the invention is prepared by encapsulating the fill using standard techniques used for

25 filling gels into such shells. Unit dosage forms comprising soft gelatin capsule shells are prepared by delivering the

- 12 -

capsule fill from the jacketed vessel, via thermostatically controlled feed tubing, to a specially adapted encapsulation machine where it is encapsulated, typically by a rotary die process, in a soft gelatin shell. The encapsulation machine 5 is suitably an RP Scherer encapsulation machine modified for filling at elevated temperature.

The soft gelatin for the shell is typically prepared batchwise by combining together glycerol, the embrittlement inhibiting composition and purified water, and transferring 10 this blend to a gelatin melter to which gelatin powder is then added. The mixture is generally blended under heat and vacuum for one to two hours until a deaerated homogeneous solution is obtained. The solution is then typically transferred to an electrically heated holding vessel, 15 maintained in the region of 60°C, to which any desired additional ingredients, such as chlorophyll, are then added.

The capsules prepared as described above are typically formulated to contain 10, 15, 20 or 30mg of the benzodiazepine temazepam. The initial mass of the fill of 20 one capsule, prior to encapsulation, is usually from 250 to 300mg, typically about 280mg. However, once encapsulation has taken place the mass of the fill generally increases due to the migration of water and a small amount of glycerol from the shell to the fill, as a consequence of the 25 hydrophilicity of the fill. Thus the total mass of the capsule fill post encapsulation is usually from 280 to

- 13 -

320mg, for example from 290 to 310mg and preferably about 300mg, preferably including 10mg of temazepam. In general the water content of the fill post encapsulation, following water ingress, is in the region of 5 to 6% by weight.

5        The capsules of the present invention provide an effective deterrent to potential intravenous drug abusers on account of the high viscosity of the capsule fill making injection at ambient temperatures impossible. The dark coloration of both the fill and the capsule shell are

10      further deterrents. There is not, however, any loss of convenience to the genuine user of the benzodiazepine. The dissolution of the drug administered in the capsules of the invention is just as good as that of the original liquid fill temazepam capsules, as illustrated by the in vitro

15      results in Figure 3 of the accompanying drawings.

Incorporating a benzodiazepine in a high viscosity polyethylene glycol blend in accordance with the present invention is therefore unlikely to have an adverse effect on the pharmacokinetic properties of the drug in vivo.

20      Example 6 which follows illustrates how the gel of the invention cannot be expelled from a syringe at ambient temperatures. This contrasts with the thickened compositions based on polyethylene glycol 400 which are shown, in Reference Example 4 which follows, to be capable

25      of being expelled from a syringe at ambient temperature.

The invention is further illustrated by the following

- 14 -

Examples. In the accompanying drawings:

Figure 1 shows the variation of viscosity with temperature for a gel of the present invention;

Figure 2 is a histogram illustrating the syringeability 5 of capsule fills based on polyethylene glycol 400;

Figure 3 compares the temazepam in vitro release characteristics of a capsule of the present invention (line X—X) with those of the original liquid fill capsule (line X—X) ; and

10 Figure 4 is a plot of viscosity against shear stress for the capsule filling of the present invention (line X—X) and for the original liquid fill formulation (line X—X).

Figure 5 is a profile showing the variation of plasma concentration of Temazepam with time for a capsule of the 15 invention (line —g—) and a reference liquid-filled capsule (line ---l---).

- 15 -

Example 1: Preparation of the Polyethylene glycol gel

A batch of the polyethylene glycol gel was prepared as follows. Polyethylene glycol 600 (172.06 kg) was weighed 5 into a jacketed mixing vessel. Polyethylene Glycol 1500 (70.00 kg) and polyethylene glycol 6000 (11.20 kg) were added to the vessel, together with glycerol (14.00 kg), and the mix was heated to about 75°C with stirring. Stirring was then continued (for approximately 1.5 hours) at this 10 temperature until a clear solution was obtained.

The blend of the three polyethylene glycols contained 67.9% by weight of polyethylene glycol 600, 27.6% by weight of polyethylene glycol 1500 and 4.4% by weight of polyethylene glycol 6000.

15 Example 2: Preparation of capsule fill

To the polyethylene glycol mix prepared according to Example 1, and brought to a temperature of about 65°C, was added temazepam (10.00 kg). Stirring in the jacketed mixing vessel was continued until the temazepam had dissolved.

20 In order to deaerate the mixture, a vacuum was applied to the mixing vessel. When the required vacuum had been achieved the vacuum was broken. Deaeration was then complete and the mixture was transferred to a thermostatically controlled jacketed vessel.

- 16 -

Example 3: Preparation of coloured capsule fill

The process of Example 2 was repeated, but after complete dissolution of the temazepam a chlorophyll solution was prepared by dissolving chlorophyll KK (0.280 kg) in warm, 5 purified water BP/EP (2.460 kg). This chlorophyll solution was added to the temazepam mixture and stirring was continued for approximately 10 minutes. The mixture was then deaerated as described in Example 2 and transferred to a thermostatically controlled jacketed vessel.

10 Reference Example 1: Preparation of soft gelatin batch for capsule shell

Glycerol (89.78 kg), Anidrisorb 85/70 (35.255 kg) and purified water BP/EP (157.116 kg) were weighed into a clean, tared and labelled stainless steel mixing vessel fitted with 15 a load cell. Gelatin powder (191.22 kg) was weighed into a second stainless steel vessel fitted with a load cell.

The water/glycerol blend was transferred to a gelatin melter, to which was then added the gelatin powder. The mixture was blended in the gelatin melter under heat and a 20 vacuum of approximately 850 millibars (for 1 to 2 hours) until a deaerated homogeneous solution was obtained. This solution was then transferred to an electrically heated stainless steel holding vessel maintained at approximately 60°C.

- 17 -

Reference Example 2: Preparation of coloured soft gelatin batch

The process of Reference Example 1 was repeated and then to the gelatin solution in the holding vessel were added 5 chlorophyll KK (0.10 kg) dissolved in water and a suspension of titanium dioxide powder (0.25 kg) in glycerol (0.75 kg). These additional ingredients were incorporated into the gelatin solution using a high speed blender, the mixture being maintained at 60°C throughout.

10 The formulation of the product was as follows:

	<u>Ingredient</u>	<u>kg per 100kg</u>	<u>% wet mass</u>	<u>kg per batch</u>
	Gelatin	40.70	40.257	191.221
	Glycerol	18.36	18.902*	89.785
	Purified Water	33.44	33.077	157.116
15	Anidrisorb 85/70	7.50	7.418	35.235
	TiO <sub>2</sub> powder	0.25	0.247	1.173
	Glycerol	0.75*	*included above	
	Chlorophyll KK	0.1	0.099	0.470
20	<b>TOTAL</b>	<b>101.10</b>	<b>100.000</b>	<b>495.000</b>

Example 4: Preparation of Capsules

The fill prepared by the process of Example 2 was delivered via thermostatically controlled feed tubing to an 25 RP Scherer encapsulation machine where it was encapsulated, by the rotary die process using a 5 oval softgel die, in the soft gelatin prepared in Reference Example 2. During the encapsulation the gelatin was lubricated to aid processing.

- 18 -

Initially, i.e. prior to water and/or glycerol ingress, the fill of each capsule weighed 280.000mg. The quantity of each component of the fill per capsule is as follows:

	<u>Ingredient</u>	<u>mg/capsule</u>
5	Temazepam	10.000
	Polyethylene Glycol 600	172.060
	Polyethylene Glycol 1500	70.000
	Polyethylene Glycol 6000	11.200
	Purified water BP/EP	2.460
	Glycerol	14.000
10	Chlorophyll KK	0.280
	<hr/>	<hr/>
TOTAL		280.000
<hr/>		<hr/>

15 The filled soft capsules produced were washed in Solvent 30 and transferred to a tumble drier, where they were tumble dried for approximately one hour in a low humidity air flow at a temperature of about 21°C. Final drying was completed by spreading the soft capsules out on shallow trays and 20 allowing them to dry in a low humidity environment.

It is to be stressed that the above formulation applies to the fill before water and/or glycerol have migrated into it from the shell. The water content will typically increase to form from 4 to 6% of the final mass of the fill, 25 and the glycerol content will increase gradually throughout the shell-life of the capsules.

- 19 -

Example 5: Testing of the Polyethylene glycol gels

Polyethylene glycol compositions of varying formulation were prepared in the laboratory by a process analogous to that of Example 1. In some cases polyethylene glycol 6000 5 was replaced by polyethylene glycol 4000. The drop point (C) of each composition was then measured using a standard Metler FP83 drop point apparatus. The results obtained are listed in Table 1 below.

TABLE 1

	<u>Formulation</u>	PEG 600 (wt %)	PEG 1500 (wt %)	PEG 4000 (wt %)	PEG 6000 (wt %)	Drop point (C)
15	A	68.0	28.0	—	4.0	48.9
	B	67.9	27.6	—	4.4	48.2
	C	66.9	28.3	—	5.9	50.3
	D	73.6	21.7	—	4.7	48.8
	E	63.3	32.6	—	4.1	49.0
	F	65.0	25.0	10.0	—	48.6
20	G	63.0	30.0	7.0	—	48.4

The variation of viscosity with temperature of formulation A was measured using a Contraves Rheomat 25 viscometer, and is illustrated in Figure 1 of the accompanying drawings.

- 20 -

Reference Example 3: Preparation of compositions based on  
PEG 400

A standard polyethylene glycol 400 temazepam formulation H, corresponding to the original liquid fill formulation 5 and shown below, was prepared by melting polyethylene glycol 400, cooling the temperature to about 45°C, then adding water and glycerol followed by temazepam. The mixture was stirred until all the temazepam had dissolved. The following quantities refer to an amount corresponding 10 to one 10mg temazepam capsule, containing 255mg of fill (prior to water or glycerol ingress).

	<u>Ingredients of H</u>	<u>mg</u>	<u>wt %</u>
	Polyethylene Glycol 400	230.00	90.196
	Glycerol	12.75	5.000
15	Water	2.25	0.883
	Temazepam	10.00	3.921
	<hr/>	<hr/>	<hr/>
	<b>TOTAL</b>	<b>255.00</b>	<b>100.00</b>
	<hr/>	<hr/>	<hr/>

20 Six formulations I to N based on H were then prepared, using the same amount of temazepam, glycerol and water but replacing part of the polyethylene glycol 400 by varying amounts of polyethylene glycols 1500, 4000 and/or 6000, as thickener. The particular polyethylene glycol blends used 25 in each formulation is shown in Table 2, which follows:

- 21 -

TABLE 2

Formulation	PEG 400		PEG 1500		PEG 4000		PEG 6000	
	mg	wt%	mg	wt%	mg	wt%	mg	wt%
5	H	230.00	100.00	—	—	—	—	—
	I	209.60	91.1	—	—	20.4	8.9	—
	J	186.65	81.2	38.25	16.6	5.10	2.2	—
	K	189.20	82.3	38.25	16.6	—	—	2.55
	L	213.90	93.0	—	—	10.35	4.5	5.75
10	M	214.59	93.3	—	—	—	—	15.41
	N	179.00	77.8	51.0	22.2	—	—	6.7

15 Reference Example 4: Testing of Compositions based on PEG 400

Formulations H to N prepared in Reference Example 3 were tested for their syringeability as follows.

A JJ tensile strength tester was used to measure the 20 compression force required to push an equivalent volume of each formulation at 20°C through a 2ml syringe and 25G needle. The syringe was filled with the sample and placed in the purpose-built holder. A load cell of 500N was lowered onto the syringe at 10mm/minute. At the instant a 25 load was registered a stop clock was started. After 3 minutes the maximum load was recorded.

The results are shown in Table 3 below and in the histogram of Figure 2 of the accompanying drawings. All the formulations were capable of being expelled from a

- 22 -

syringe at ambient temperature.

TABLE 3

		Average Force (n=3)		
	Formulation	Newtons	(S.D.,	C.V.)
5	H	13.7	(0.6,	4.2)
	I	38.7	(0.6,	1.5)
	J	55.7	(1.2,	2.1)
	K	59.3	(1.2,	1.9)
10	L	29.0	(1.0,	3.4)
	M	40.7	(2.1,	5.1)
	N	69.3	(1.2,	1.7)

15 Example 6: Further testing of the Polyethylene glycol gels

Temazepam capsules comprising formulation A of the invention, prepared in Example 5, were compared with temazepam capsules comprising formulation H, prepared in Reference Example 3, with respect to their properties of 20 dissolution (temazepam release). The viscosity of formulations A and H were then compared and finally the syringeability of formulation A was compared with that of formulations H to N based on polyethylene glycol 400, as described in Reference Examples 3 and 4.

25 Dissolution

The dissolution of 20mg temazepam capsules comprising A, and 20mg temazepam capsules comprising H, was determined using the U.S.P. dissolution test. Dissolution was

- 23 -

measured in 0.1M HCl using a standard flow through technique (Apparatus: Apple II Europlus Microcomputer; LKB Ultrospec 4052 TDS Spectrophotometer; Caleva Dissolution Apparatus, model 6ST; and Watson-Marlow 5025 Peristaltic Pump. Parameters: USP Paddle method at 100 r.p.m.; dissolution medium, 0.1M HCl; bath temperature, 37°C; run time, 10 minutes; sample time, 1 minutes; and wavelength, 230nm).

The dissolution profiles (average of 6 individual determinations) are shown in the graph of % temazepam release against time in Figure 3 of the accompanying drawings. The profiles indicates that there is no reduction in temazepam release from capsules comprising formulation A as compared with capsules comprising formulation H, containing only polyethylene glycol 400.

Viscosity

The flow properties of formulations A and H, after encapsulation, were compared by measuring the variation of viscosity with shear stress for each using a Carri-Med CSL 20 Rheometer.

The results are shown in the graph in Figure 4 of the accompanying drawings. The graph clearly demonstrates the superiority of formulation A of the invention over formulation H in an application where high viscosity is 25 needed.

- 24 -

Syringeability

At ambient temperature (20°C) it proved impossible to draw formulation A up into a 2ml syringe, or to inject it through a 25G needle. Measurement of the compression force required to pass the formulation through such a needle, by the method described in Reference Example 4, also proved impossible at ambient temperature since the needle was consistently blown off. It proved necessary to increase the temperature of Formulation A to at least 50°C (see Figure 2) for it to begin to exhibit the viscosity and syringeability characteristics of the unthickened polyethylene glycol 400 formulation H.

Example 7: Pharmacokinetic study of Temazepam Capsules

A study was carried out to define and to compare the pharmacokinetic characteristics of Temazepam capsules of the invention with conventional liquid-filled capsules, which are subject to intravenous abuse, following their oral administration to human subjects.

The open, randomized, cross-over study involved administration to 24 healthy volunteers of a unit dosage form of the invention, comprising Temazepam in a soft gelatin capsule, and of a liquid-filled reference formulation of Temazepam. In each case a single oral dose of 20mg of the drug was provided.

The results of the study are shown in accompanying Figure 5, in which the line (—g—) denotes capsules of the

- 25 -

invention (TG) and the line (---1---) denotes the reference formulation (TL).

The relative bioavailability of the two formulations assessed in terms of the area under the time versus plasma 5 concentration profile is not significantly different from parity and lies well within the acceptable 80-120% limits for bioequivalence. Although the mean Cmax for TG (616.6ng/ml) may be 12.9% lower than for TL (707.9ng/ml) and the median time to reach Cmax (Tmax) is 40 min (TG) vs 10 30 min (TL), there is no significant difference between TG and TL either in their absorption constant (Ka) (0.123 vs 0.138 min-1 respectively) or their distribution (alpha) (29.5 vs 32.4 min) and elimination (beta) (6.3 vs 6.6 h) half-lives.

15 The results therefore show that the increased viscosity of the capsule fill in the unit dosage form of the invention does not adversely affect the pharmacokinetic characteristics of the encapsulated Temazepam. In particular a rapid rise in plasma concentration followed by 20 a prompt fall is seen to be conserved, which is essential for the use of Temazepam as a hypnotic and premedicant.

- 26 -

C L A I M S

1. A pharmaceutical unit dosage form comprising a soft gelatin capsule shell or a two-piece hard gelatin capsule and a fill comprising a benzodiazepine dissolved or suspended in a gel, wherein the gel has a drop point (C), prior to encapsulation, of at least 46 and comprises at least 63% by weight of polyethylene glycol 600, at least 2% by weight of polyethylene glycol 4000 or 6000 and at least 21% by weight of an intermediate polyethylene glycol, the 10 total amount of polyethylene glycol in the gel being 100%.

2. A unit dosage form according to claim 1 wherein the intermediate polyethylene glycol is polyethylene glycol 1500.

3. A unit dosage form according to claim 1 or 2 15 wherein the gel comprises 67 to 68% by weight of polyethylene glycol 600, 27 to 28% by weight of polyethylene glycol 1500 and 4 to 6% by weight of polyethylene glycol 6000.

4. A unit dosage form according to any one of the 20 preceding claims, wherein the gel has a drop point prior to encapsulation of 48C to 60C.

5. A unit dosage form according to claim 4, wherein the drop point is from 48.2C to 50.3C.

6. A unit dosage form according to any one of the 25 preceding claims wherein the fill further comprises glycerol or any other co-solvent.

- 27 -

7. A unit dosage form according to claim 6 wherein the fill comprises from 2 to 20% by weight of glycerol.

8. A unit dosage form according to any one of the 5 preceding claims wherein the benzodiazepine is temazepam.

9. A unit dosage form according to any one of the preceding claims wherein the fill further comprises a pigment or dye.

10. A unit dosage form according to claim 9 10 wherein the pigment is chlorophyll.

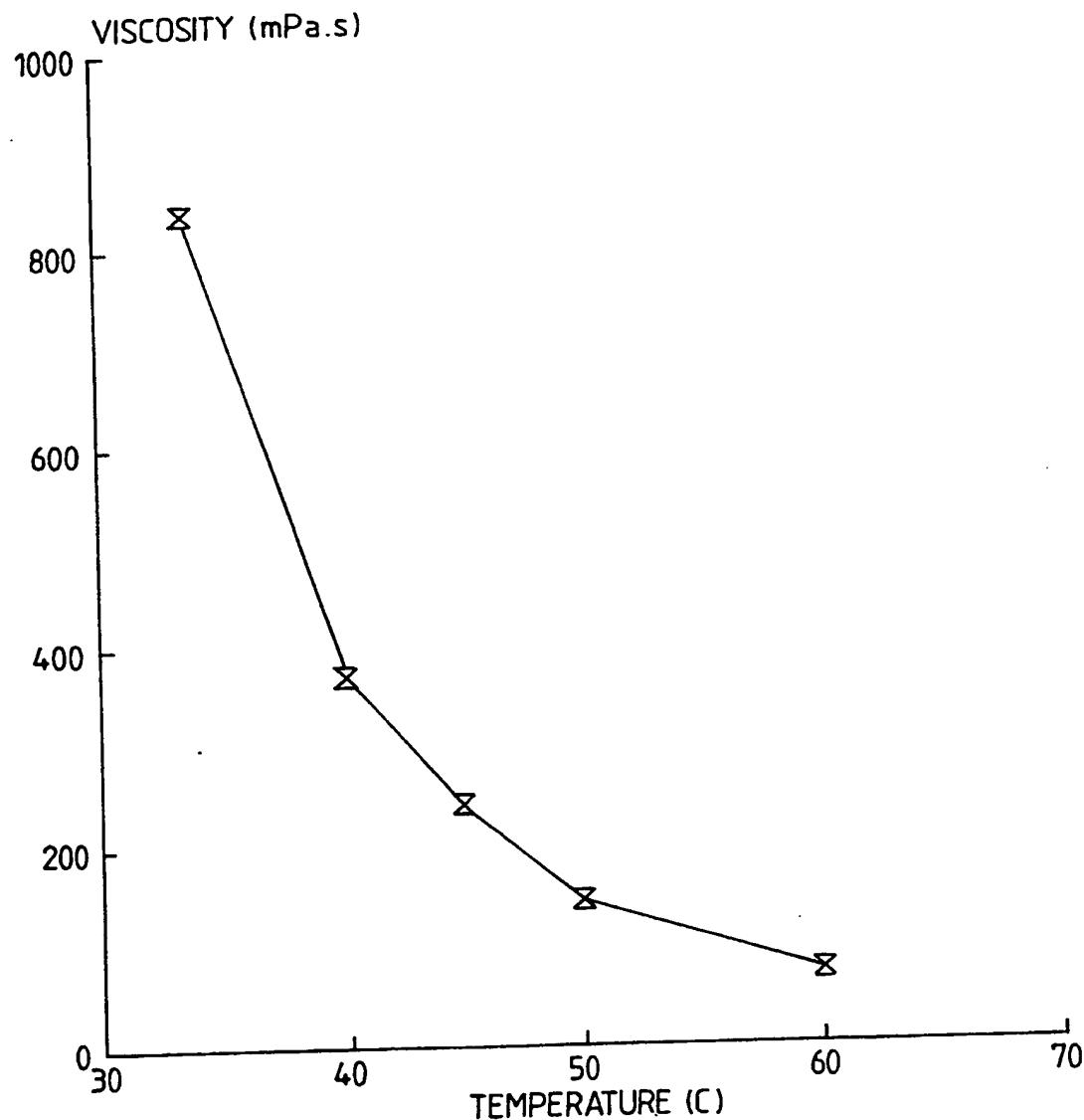
11. A process for the preparation of a pharmaceutical unit dosage form as claimed in any one of claims 1 to 10, which process comprises:

a) preparing a polyethylene glycol blend by 15 combining at least 63% by weight of polyethylene glycol 600, at least 2% by weight of polyethylene glycol 4000 or 6000 and at least 21% by weight of an intermediate polyethylene glycol;

b) forming a fill by dissolving or suspending a 20 benzodiazepine in the polyethylene glycol blend, and c) encapsulating the fill in a soft gelatin capsule shell or a two-piece gelatin capsule.

~~111~~

Fig.1.



SUBSTITUTE SHEET

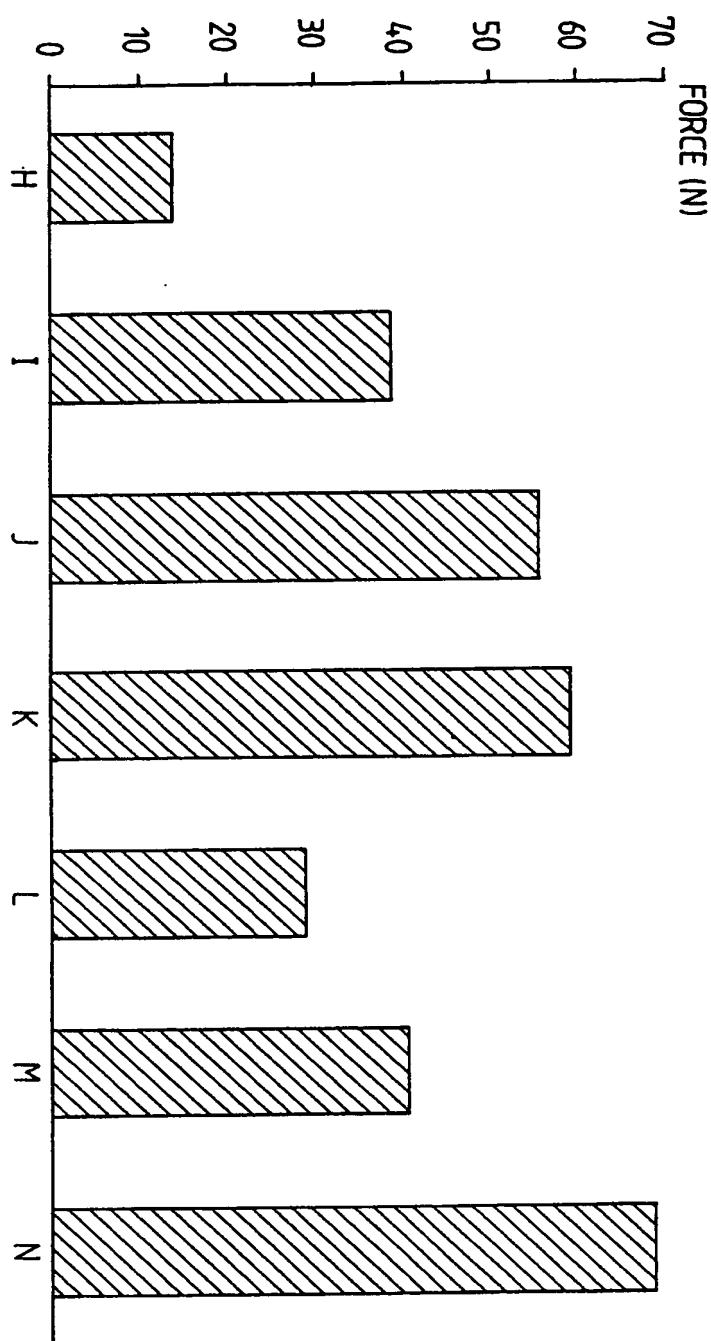


Fig.2.

2/4

SUBSTITUTE SHEET

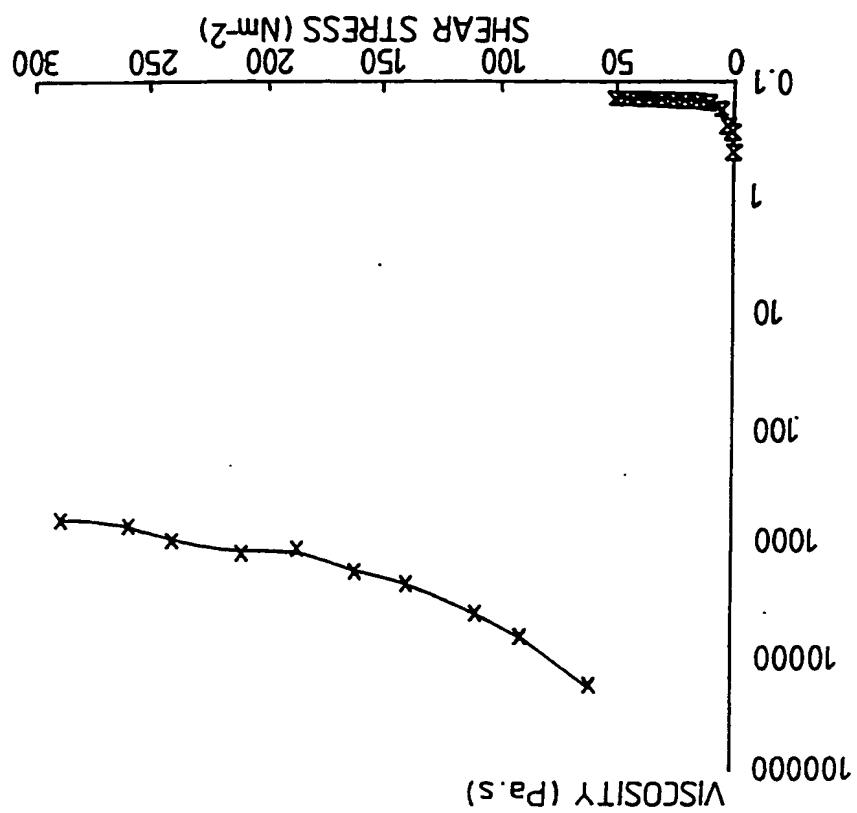


Fig. 4.

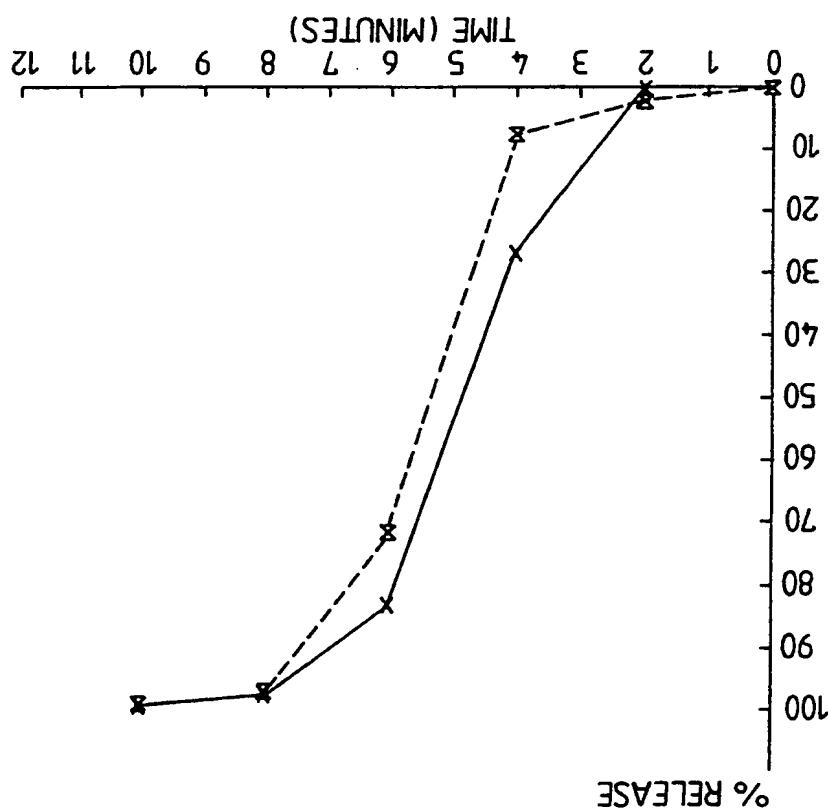


Fig. 3.

3/4

SUBSTITUTE SHEET

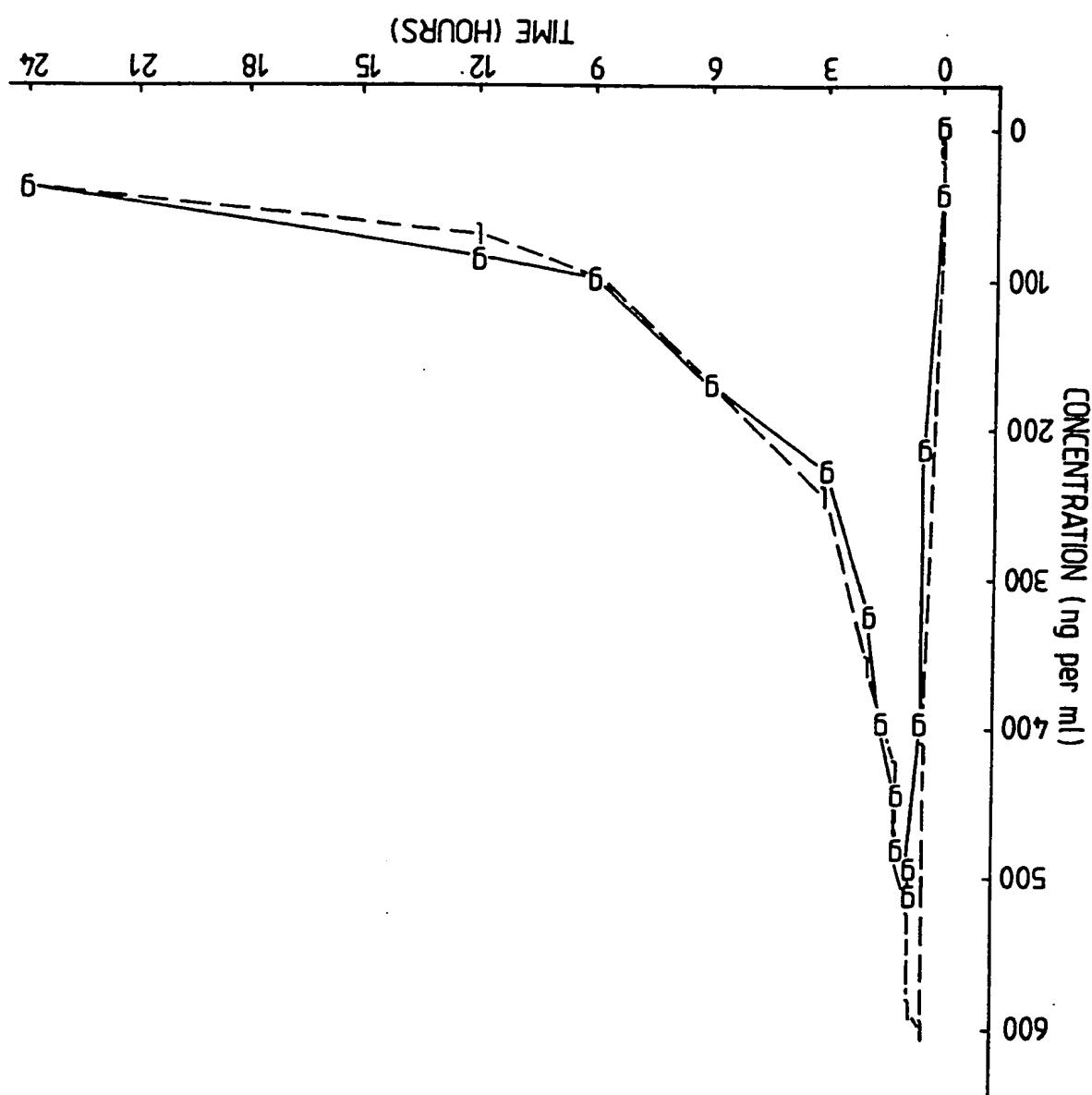


Fig. 5.

44

INTERNATIONAL SEARCH REPORT		INTERNATIONAL CLASSIFICATION OF SUBJECT MATTER (if several) CLASSIFICATION SYMBOLS APPROPRIATE TO BOTH NATIONAL CLASSIFICATION AND IPC	
IPC <sub>5</sub> : A 61 K 9/48, 9/66, 47/10, 31/55		ACCORDING TO INTERNATIONAL PATENT CLASSIFICATION (IPC) OR TO BOTH NATIONAL CLASSIFICATION AND IPC	
Information Applicable to		Information Applicable to	
II. FIELDS SEARCHED		Classification System	
IPC <sub>5</sub>		Classification System	
A 61 K		Minimum Documentation Search	
Documented other than Minimum Documentation		Documentation Search	
III. DOCUMENTS CONSIDERED TO BE RELEVANT		Category	
EP, A, 0120248 (R.P. SCHERRER GMBH)		Citation of Document, "With Indication, Where Appropriate, of the Relevant Passages" is Relevant to Claim No. 13	
3 October 1984		See page 1, Lines 1-4; Page 6, Lines 7-25; Page 10, Lines 3-12; Pages 12, 13, example 1, claims 1, 3, 4	
EP, A, 0152292 (R.P. SCHERRER CORPORATION)		See page 1, Lines 1-4; Page 6, Lines 7-25; Page 10, Lines 5, 13 - Page 6, Lines 2-4; Page 5, Lines 13 - Page 6, Lines 5; Pages 16, 17, example 1, claims 1-9, 11	
21 August 1985		See page 2, Lines 15-23; Page 4, Lines 14-18; Page 5, Lines 1-18; Page 7, example 1; claims 1, 4	
DE, A, 2614864 (SCHWABE W.)		See page 2, Lines 15-23; Page 4, Lines 14-18; Page 5, Lines 1-18; Page 7, example 1; claims 1, 4	
13 October 1977		---	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		Y	
EP, A, 0152292 (R.P. SCHERRER CORPORATION)		EP, A, 0152292 (R.P. SCHERRER CORPORATION)	
21 August 1985		See page 1, Lines 1-4; Page 6, Lines 7-25; Page 10, Lines 5, 13 - Page 6, Lines 2-4; Page 5, Lines 13 - Page 6, Lines 5; Pages 16, 17, example 1, claims 1-9, 11	
Y		See page 2, Lines 15-23; Page 4, Lines 14-18; Page 5, Lines 1-18; Page 7, example 1; claims 1, 4	
DE, A, 2614864 (SCHWABE W.)		See page 2, Lines 15-23; Page 4, Lines 14-18; Page 5, Lines 1-18; Page 7, example 1; claims 1, 4	
1-7, 11		1-7, 11	
Y		---	
III. DOCUMENTS CONSIDERED TO BE RELEVANT		Category	
EP, A, 0120248 (R.P. SCHERRER GMBH)		Citation of Document, "With Indication, Where Appropriate, of the Relevant Passages" is Relevant to Claim No. 13	
3 October 1984		See page 1, Lines 1-4; Page 6, Lines 7-25; Page 10, Lines 3-12; Pages 12, 13, example 1, claims 1, 3, 4	
EP, A, 0152292 (R.P. SCHERRER CORPORATION)		See page 1, Lines 1-4; Page 6, Lines 7-25; Page 10, Lines 5, 13 - Page 6, Lines 2-4; Page 5, Lines 13 - Page 6, Lines 5; Pages 16, 17, example 1, claims 1-9, 11	
21 August 1985		See page 2, Lines 15-23; Page 4, Lines 14-18; Page 5, Lines 1-18; Page 7, example 1; claims 1-9, 11	
Y		See page 2, Lines 15-23; Page 4, Lines 14-18; Page 5, Lines 1-18; Page 7, example 1; claims 1, 4	
DE, A, 2614864 (SCHWABE W.)		See page 2, Lines 15-23; Page 4, Lines 14-18; Page 5, Lines 1-18; Page 7, example 1; claims 1, 4	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
EP, A, 0152292 (R.P. SCHERRER CORPORATION)		EP, A, 0152292 (R.P. SCHERRER CORPORATION)	
21 August 1985		See page 1, Lines 1-4; Page 6, Lines 7-25; Page 10, Lines 5, 13 - Page 6, Lines 2-4; Page 5, Lines 13 - Page 6, Lines 5; Pages 16, 17, example 1, claims 1-9, 11	
Y		See page 2, Lines 15-23; Page 4, Lines 14-18; Page 5, Lines 1-18; Page 7, example 1; claims 1-9, 11	
DE, A, 2614864 (SCHWABE W.)		See page 2, Lines 15-23; Page 4, Lines 14-18; Page 5, Lines 1-18; Page 7, example 1; claims 1, 4	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11		1-7, 11	
Y		---	
DE, A, 2614864 (SCHWABE W.)		DE, A, 2614864 (SCHWABE W.)	
1-7, 11			

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category	Citation of Document, " with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	GB, A, 2185887 (FARMITALIA CARLO ERBA LTD) 5 August 1987 see claims 19,20 ---	9,10
P,A	Manufacturing Chemist, volume 60, no. 12, December 1989, (Woolwich, London, GB), A.P. Launchbury et al.: "The development of temazepam gelthix", page 38-40 -----	

ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.

GB 9001821  
SA 42128

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 12/03/91. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0120248	03-10-84	DE-A, C AU-B- AU-A- CA-A- JP-T- WO-A- US-A-	3307353 567448 2690384 1211712 60500623 8403417 4744988	06-09-84 19-11-87 28-09-84 23-09-86 02-05-85 13-09-84 17-05-88
EP-A- 0152292	21-08-85	AU-A- JP-T- NL-T- WO-A-	3880185 61501202 8520012 8503439	27-08-85 19-06-86 02-01-86 15-08-85
DE-A- 2614864	13-10-77	None		
GB-A- 2185887	05-08-87	DE-A- CH-A-	3705074 671881	01-09-88 13-10-89